CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-128

ADMINISTRATIVE DOCUMENTS

13.0 Patent Information

1. General
   a. Patent Number and Expiration Date
      5,374,659 Expiration December 20, 2011

   b. Type of Patent:
      Formulation

   c. Name of Patent Owner
      McNeil-PPC, Inc.

   d. US Agent
      McNeil-PPC, Inc.

2. Declaration (for formulation, composition, or method of use patents)

   The undersigned declares that Patent No. 5,374,659 covers the formulation, composition, and/or method of use of Children's MOTRIN® Cold Suspension. This product is submitted for approval in this new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act.

   Name 
   Joseph F. Leightner
   Title Patent Attorney
   Registration Number 34, 209
   Date September 28, 1999

APPEARS THIS WAY
ON ORIGINAL

14.0 Patent Certification

To the best of applicant's knowledge this product and process is not covered by any other enforceable patent.

Name
Joseph F. Leightner
Title Patent Attorney
Registration Number 34, 209
Date September 28, 1999

EXCLUSIVITY SUMMARY for NDA # 21-128 SUPPL # _____
Trade Name Children's Motrin Cold Suspension
(100 mg/5mL)(15mg/5mL)
Generic Name ibuprofen suspension
Applicant Name McNeil Consumer Healthcare HFD-550
Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/X/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /X/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /X/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      The sponsor submitted 2 pharmacokinetic studies and 1 safety study

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /X/ NO /__/ The Unknown item

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

6 months pediatric exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/ denied

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An

active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-001 Motrin Chewable Tablets

NDA # 20-602 Jr. Strength Motrin

NDA # 20-603 Children's Motrin Suspension

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

yes, Safety only.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /X/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

   a safety study was required for the combination.

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 99-056 - Safety study

Investigation #2, Study # 98 057 - PK-Study

Investigation #3, Study # 97-524 - PK study

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 99-056 - Safety

Investigation #2, Study # 98-057 PK

Investigation #3, Study # 97-024 PK

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND #(_____) YES /_X_/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND #(_____) YES /_X_/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

/S/ 8/1/00

Signature of Preparer Date

Title: Project Manager

/S/ 8/1/00

Signature of Office of Division Director Date

cc:
Archival NDA
HFD- /Division File

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21128	**Trade Name:**	CHILDRENS MOTRIN COLD SUSPENSION
Supplement Number:	-	**Generic Name:**	IBUPROFEN (100MG/5ML) PSEUDOEPHEDRINE HC
Supplement Type:		**Dosage Form:**	Suspension; Oral
Regulatory Action:	AP	**Proposed Indication:**	for the temporary relief of nasal and sinus congestion, minor body aches and pains, fever, stuffy nose, headache, and sore throat

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) _X_Children (25 months-12 Years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for ALL pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, SANDRA COOK

/S/

Signature

7/27/00

Date

APPEARS THIS WAY ON ORIGINAL

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 9/7/99. Application Written Request was made to: NDA/IND

Timeframe Noted in Written Request for Submission of Studies 6/1/01.

NDA# 21-128 Supplement #_____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR

Sponsor McNeil Consumer Healthcare

Generic Name Ibuprofen/Pseudoephedrine HCl suspension, 100 mg/5 mL, 15 mg/5 mL

Trade Name Children's Motrin Cold Suspension

Strength _____ Dosage Form/Route Suspension/Oral

Date of Submission of Reports of Studies 9/30/99. Date Received: 10/01/99

Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 12/30/99.

Was a formal Written Request made for the pediatric studies submitted?	Y X	
Were the studies submitted after the Written Request?	Y X	
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y X	
Was the timeframe noted in the Written Request for submission of studies met?	Y X	
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y X	
Were the studies responsive to the terms of the Written Request?	Y___	

[redacted]

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ___**Granted** ✓**Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date

Pediatric Exclusivity will apply to all patents and exclusivities granted upon approval of NDA 21-128

SIGNED /S/ _____ DATE 12/6/99

cc:

Archival NDA 21-128

HFD-550/division file
HFD-550/Middhun/Hyde
HFD-550/Villalba
HFD-880/Adebowale
HFD-550/RPM/Cook
HFD-93/Division of Data Management Services
HFD-600/Office of Generic Drugs
HFD-2/M.Lumpkin
HFD-104/D.Murphy

16.0 Debarment Certification

McNeil Consumer Healthcare hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Name: Jacqueline U. Linse

Title: Associate Director
Regulatory Affairs

Date: 6/22/00

REVISED

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved OMB No. 0910-0338
Expiration Date April 30, 2000
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
McNEIL CONSUMER HEALTHCARE	APR 27 2000
TELEPHONE NO *(Include Area Code)* (215) 273-8368	FACSIMILE (FAX) Number *(Include Area Code)* (215) 273-4049
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Camp Hill Road, Fort Washington, PA 19034	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE: Camp Hill Road, Fort Washington, PA 19034

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-128

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Ibuprofen/Pseudoephedrine HCl	Children's Motrin Cold Suspension

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)* –

DOSAGE FORM: Suspension	STRENGTHS: (100mg/5mL) (15mg/5mL)	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE: Temporarily relieve symptoms associated with the common cold, flu or sinusitis including nasal and sinus congestion, stuffy nose, headache, sore throat, body aches and pains and to temporarily reduce fever.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Labeling Amendment No. 4

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*			
	1 Index		
X	2. Labeling (check one)	☒ Draft Labeling	☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))		
	4. Chemistry section		
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)		
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)		
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)		
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)		
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)		
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))		
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)		
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)		
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)		
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)		
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)		
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))		
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))		
	15. Establishment description (21 CFR Part 600, if applicable)		
	16. Debarment certification (FD&C Act 306 (k)(1))		
	17. Field copy certification (21 CFR 314.50 (k) (3))		
	18. User Fee Cover Sheet (Form FDA 3397)		
	19. OTHER (Specify)		

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Janet A. Uetz	Janet A. Uetz, Associate Director, Regulatory Affairs	APR 27 2000

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
Camp Hill Road Fort Washington, PA 19034	(215) 273-8368

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21128/000
Stamp: 01-OCT-1999 Regulatory Due: 01-AUG-2000
Applicant: MCNEIL CONS

Priority: 3S Org Code: 550
Action Goal: District Goal: 02-JUN-2000
Brand Name: CHILDRENS MOTRIN COLD SUSPENSION
Established Name:
Generic Name: IBUPROFEN (100MG/5ML) PSEUDOEPHEDRINE HC
Dosage Form: SUS (SUSPENSION)
Strength: 100MG/5ML, 15MG/5ML

FDA Contacts:
S. COOK (HFD-550) 301-827-2090 , Project Manager
R. PUTTAGUNTA (HFD-830) 301-827-0968 , Review Chemist
M. ZARIFA (HFD-120) 301-594-2850 , Team Leader

Overall Recommendation:

ACCEPTABLE on 13-MAR-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-DEC-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-DEC-1999
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: 2510184
MCNEIL CONSUMER PRODUCTS CO
1 CAMP HILL RD
FORT WASHINGTON, PA 19034
DMF No:
AADA No:

Profile: LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Milestone Date: **13-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**OPDRA POSTMARKETING SAFETY REVIEW** JUL 18 2000	
TO: Division of OTC Drug Products (HFD-560) Charles J. Ganley, M.D., Director	**FROM: DDRE I (HFD-430)**	**OPDRA PID #** D000279
DATE REQUESTED: March 27,2000 **DATE RECEIVED:** March 27, 2000	**REQUESTOR/Phone #:** Linda Hu, M.D. Medical Officer, Div. of OTC Drug Products POC: Marina Chang, R.Ph, ext 7-2305	
DRUG (Est): Pseudoephedrine Ibuprofen	**NDA/IND #** Multiple	**SPONSOR:** Multiple
DRUG NAME (Trade): Multiple	**THERAPEUTIC CLASSIFICATION:** Decongestant / NSAID	

EVENT: All reports for drug interactions in pediatrics (ages 2-12 years) reported since 9/1/1997
Note: Per requestor, date was expanded to include all ibuprofen – pseudoephedrine reports for ages 2-12.

EXECUTIVE SUMMARY: A July 7, 2000 AERS search found a total of 12 cases reported between 1994 and the present in which ibuprofen and pseudoephedrine were being taken concomitantly in 2-12 year old patients. A review of these 12 cases found no identifiable cases of drug interaction between ibuprofen and pseudoephedrine.

REASON FOR REQUEST/REVIEW: To support the OTC safety review of new NDA 21[ ]for ibuprofen/ pseudoephedrine oral suspension. This is the first NDA for a pseudoephedrine/ibuprofen combination product for pediatric use.

RELEVANT PRODUCT LABELING: Current labeling for products containing either drug or both does not contain any information regarding drug interactions between ibuprofen and pseudoephedrine.

USAGE INFORMATION: Not Applicable

SEARCH DATE: July 7, 2000 | **SEARCH TYPE(S):** X AERS (Drug Interaction) X Literature Other _____

SEARCH CRITERIA: Drug Names: Ibuprofen and Pseudoephedrine (to include any trade names, verbatims)
MEDDRA Terms: All Dates: All

Note: An initial search using the trade names of the two combination products containing ibuprofen and pseudoephedrine (Sine-Aid IB, Advil Cold and Sinus), returned six cases. None of the cases were in patients < 12 years old and none appeared to be a drug interaction.

SEARCH RESULTS: No Medline literature references to a pseudoephedrine-ibuprofen interaction were found. Twelve cases were found in which ibuprofen and pseudoephedrine were used concomitantly in 2-12 year old patients. See Attachment (1) for case summaries.

DISCUSSION / CONCLUSIONS: (SEE ATTACHMENT FOR CASES NUMBERS) Of the 12 cases reviewed, none reported a suspected drug interaction between pseudoephedrine and ibuprofen. In two of the cases (#2, 11) that listed "No Drug Effect" as the event, it is not possible to tell if this is drug interaction related. In two cases (#1, 12), other drugs [ ]Zithromax) appear to be the causative agent for the reported reaction. In six cases (#3, 4, 5, 6, 8, 10), the ibuprofen product alone appears to be the causative agent. In one case (#9) Allegra D (a pseudoephedrine-containing product) is the primary suspect agent. In the one remaining case (#8), the patient took both drugs for the same two-day period and it is not possible to differentiate the reason for the patient's "itchy feet."

This case series shows the difficulty of determining whether the reported event is due to a drug interaction, one of the agents alone, or a concomitant drug the patient may have been taking. Drugs listed as concomitant medications do not usually include dates of therapy, which makes it impossible to determine a temporal relationship to the event for one of the specific drugs. Although we can not exclude the possibility of a drug teraction, there was no evidence or suspicion in the 12 cases that the events reported were due to a drug eraction between ibuprofen and pseudoephedrine.

These results were conveyed (via email) to Ms. Marina Chang and Dr. Linda Hu, M.D. on July 10, 2000.

REVIEWER'S SIGNATURE / DATE:	**TEAM LEADER'S SIGNATURE / DATE:**
Michael F. Johnston, R.Ph. 7/17/2000	Claudia Karwoski, Pharm.D. 7/18/2000 /S/

DIVISION DIRECTOR SIGNATURE / DATE:	OFFICE DIRECTOR SIGNATURE / DATE:
Julie Beitz, M.D.	

ATTACHMENTS:

Case Summaries for All Cases: Pseudoephedrine and Ibuprofen (Potential Drug Interaction)

Cc: HFD-560 (Division File)/MChang, LHu
HFD-430 Drug Files Electronic Copy: CKarwoski/ATrontell/JBeitz/MJohnston/PGuinn
HFD-400 (Electonic Copy): PHonig

Electronic File Name:

ATTACHMENT (1): Case Summaries for All Cases: Pseudoephedrine and Ibuprofen (Potential Drug Interaction) with Discussion

(In Chronological Order of FDA Received Date)

1. **(FDA #1539137, Direct, 7/94, CA, Serious Report)** A 6 year-old hospitalized male reported an injection site inflammation after IV [redacted] Advil and Sudafed were listed as concomitant medications and had been used to treat the inflammation (not suspect).

2. **(FDA #1785756, McNeil #0496446A, 4/96)** A 6 year-old male reported "no drug effect" after eight days of Children's Motrin Suspension. Patient reported as taking concomitant [redacted] (contains pseudoephedrine).

3. **(FDA #1786291, McNeil #2550876A, 4/96A, 4/96)** A 7 year-old female reported hives on the leg after one day of Children's Motrin Suspension. Medical history included asthma with no known drug allergies. Concomitant medications included Ventolin, Intal, Sudafed, and Robitussin.

4. **(FDA #1800334, McNeil #1589104A, 7/96)** A 6 year-old female reported blisters on the fingertips after two days of Children's Motrin Suspension. Medical history included recent upper respiratory infection with concomitant medications of erythromycin/sulfisoxazole, and [redacted] (contains pseudoephedrine). No known drug allergies.

5. **(FDA #1847838, Schwartz #002#4#1996-00378, KY, 8/96, Serious Report)** A 7 year-old female reported hyperkinesia (body thrashing side to side), hyperventilation (rate =100), and dyspnea ("problems breathing like the airway was closing", SAO2 =95-99%) after one 100 mg dose of Children's Motrin Suspension and [redacted] (contains pseudoephedrine). The patient was treated with cromolyn nebulizer and taken to ER and treated with Valium IV. The next day after hospital admission, she received another dose of Motrin Children's suspension and within three minutes experienced similar symptoms. Medical history included a hospitalization on the day preceding the event for radius reduction, reactive airway disorder (no history of aspirin allergy), and allergy to wheat and milk. The event was considered to be a reaction to ibuprofen due to the positive rechallenge to ibuprofen (without pseudoephedrine the second time).

6. **(FDA #1863249, McNeil #0620778A, 10/96)** A 9 year-old male reported tachycardia on two occasions after taking Children's Motrin Susp. The child's parent reported that tachycardia resolved after discontinuation of the Motrin product. Pseudoephedrine was listed as concomitant medication (no temporal information provided). Medical history included asthma and other allergies (cats, dogs, tree pollen).

7. **(FDA #1968912, McNeil #0736075A, 4/97)** A 2-1/2 year-old male reported a nosebleed after two days of Children's Motrin Susp. Sudafed was listed as a concomitant medication.

8. **(FDA $3076102-1-00, McNeil #067599A, 1/98)** A 5 year-old male reported "itchy feet" after taking Children's Motrin Susp. and Robitussin PE (contains pseudoephedrine) for two days. Both products were discontinued and the event resolved. There was no reported medical history or other medications.

9. (FDA #3321993-X-00-01, HMR #199910717HMRI, WI, 4/99) An 11 year-old female reported "hyper feeling", inability to sleep, and paranoid feeling (feeling like she would die) six hours after one dose of Allegra D. Advil was listed as a concomitant medication. Medical history included asthma, bronchial tube spasm, and fever.

10. (FDA #3285322-2-00-01, McNeil #1123594A, 6/99) A 6 year-old male reported stomatitis (burning in the mouth) for two days after starting Jr. Strength Motrin Chewable Tablets. The symptoms subsided after drinking water. Medical history included cystic fibrosis, asthma, and an unspecified reflux condition. Concomitant medications included Prilosec, Propulsid, inhalers, and Claritin D (contains pseudoephedrine).

11. (FDA #3332798-8-00-01, McNeil #1131907A, 8/99) A 5 year-old female reported no drug effect after five days of taking Children's Motrin Susp. and Children's Tylenol Cold Plus Cough Liquid for fever.

12. (FDA #3425632-9-00-01, Pfizer #9911901, TN, 12/99) A 6 year-old female reported rash (on face and hip) and peripheral edema after two days of Zithromax Pediatric Oral Susp. therapy. Pseudoephedrine and Motrin were listed as concomitant medications and both were taken prior to and after Zithromax without problem. The patient had a history to previous antibiotic therapy including amoxicillin, Lorabid, and Septra but had taken Zirthromax four times before without a problem.

APPEARS THIS WAY
ON ORIGINAL

FDA MINUTES OF SPONSOR MEETING

PRODUCT NAME: Ibuprofen/Pseudoepedrine HCl
DATE: 7/30/97
SPONSOR: McNeil Consumer Products Company

McNeil: V. Chester, J. Codispoti, M. Denisco, C. Gelotte, BJ Lavine, T. Mrazik, W. Pagsuyuin, M. Shah

FDA: M. Weintraub, D. Bashaw, M. Chang, S. Cook, B. Dunn, C. Fang, L. Hu, J. Hyde, H. Leung, S. Lin, L. Katz, M. Kennedy, S. Mason, R. Neuner, H. Patel, M. Walling, R. Widmark, C. Yaciw

SUBJECT: McNeil requested a meeting with FDA to discuss the OTC suitability of a combination ibuprofen/pseudoepedrine HCl pediatric product.

Sponsor meeting objectives:

Discuss the suitability of the ibuprofen/pseudoepedrine HCl (PSE) combination product for pediatric use.

Discuss proposed clinical development program to support OTC approval.

- FDA agrees that overall safety and efficacy have been established in adults. The half-life for PSE in children is approximately 3 hours, while the half-life in adults is approximately 6 hours. FDA will require an interaction pharmacokinetics study in children, preferrably using a solution formulation. The children's trial can be conducted in the intended population.

- FDA agrees with the proposal for the adult program to establish bioequivalence.

- FDA noted that the dosing regimen is different from the OTC ibuprofen product. The sponsor will need to justify a deviation from the currently approved dosing regimen.

- [redacted]

- [redacted]

- Full CMC and stability data would be required [redacted]

FDA made the following labeling recommendations:

- [redacted]
- Modify the aspirin warning using the most current version. Use the complete MAO warning.
- Combine the current warnings for ibuprofen and pseudoephedrine into the new OTC format.
- Include poison control center in the "Poison Control" warning.

/S/

Sandra N. Cook
Consumer Safety Officer

Memorandum

To: Charles Ganley, M.D., Tom Parmalee (Project Manager)
From: Abi Adebowale, Ph.D. 08/01/00
Through: E. Dennis Bashaw, Pharm. D. Team Leader 8/1/00
Date: 06/27/00
Subject: NDA 21-128, Children's Motrin® Cold Suspension (Ibuprofen 100 mg/5 ml and Pseudoephedrine 15 mg/5ml)

At an internal meeting on the 28th of March 1999, possible pediatric dosing regimens for this combination product were discussed. The current dosing schedule for pseudoephedrine as specified in the tentative final monograph for OTC oral nasal decongestant drug products is the "2 tier" dosing schedule (see Table1 below). The "tier" here refers to the number of dosing levels present for children aged 2 to less than 12 years of age. The proposed OTC dosing for the pediatric combination suspension is based on the proposed OTC pediatric dosing for children's ibuprofen suspension also referred to as the "5 tier" dosing schedule (see Table 2 below).

Table 1. Current OTC Dosing of Pseudoephedrine

Age	Dose	Max dose/24 hours
<2 yrs	Consult doctor	
2-5 yrs	15 mg	60 mg
6-11 yrs	30 mg	120 mg
≥12 yrs	60 mg	240 mg

The current ("5 tier") dosing schedule for OTC pediatric ibuprofen (ibu) suspension is summarized in Table 2.

Table 2. Current Pediatric Dosing of Children's Ibuprofen Suspension (100mg/5ml)

Weight (lbs)	Age (yr)	Dosage (mg)	Dose per Unit Weight (mg/kg)
under 24	under 2		Consult Doctor
24-35	2 to 3	100	6.3 - 9.2
36-47	4 to 5	150	7.0 - 9.2
48-59	6 to 8	200	7.5 - 9.2
60-71	9 to 10	250	7.7 -9.2
72-95	11	300	6.9 - 9.2

The clinical division decided that since there is little data to support the safety and efficacy of pseudoephedrine using the "5 tier" schedule, the " 2 tiered" dosing would be the best approach as it is the dosing schedule of the monograph. It was also stated that

the "2-tiered" dosing schedule would maintain the ibuprofen dosing ranges for pediatric ibuprofen of 5 – 10 mg/kg (recommended Rx dose range), except for the heaviest children within each listed age group (i.e. those who weigh 45-47 lbs and 89-95 lbs), who will be slightly underdosed, and this may be a concern. It was noted that the range of doses for ibuprofen extends lower for the combination suspension product (4.6 mg/kg) than for the currently approved single-ingredient OTC pediatric ibuprofen product.

At this point Dr. Bashaw presented the PK/PD data that was generated for NDA 20-135 (see attachment). In this study children with fever were given ibuprofen doses of either 5 or 10mg/kg. While the hysteresis loops and subsequent estimates of EC50 are highly variable, it is apparent from the data that in these subjects a higher dose was not necessarily associated with a higher degree of temperature reduction. It did, however, tend to correlate with a longer duration of action. Based on this data it was then decided that an earlier proposal to restrict dosing from 6-8hrs to 6hrs only would be appropriate as with more frequent dosing there would be some accumulation of drug that would "re-inforce" the lower doses.

CC:
NDA 21-128 (Memorandum)
HFD-550 (Div. File)
HFD-550 (CSO/Cook)
HFD-560 (Div. File)
HFD-560 (CSO/Parmalee)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Adebowale)
HFD-340 (Viswanathan)

2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

Cook

FACSIMILE TRANSMISSION RECORD

Center for Drug Evaluation and Research
FDA

From: Sandra Cook KM

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

Phone 301-827-2040
Fax 301-827-2531

Date: 3/9/00

To:

Name Janet Uti
Company McNeil
City ______ State ____
Phone # 215 273 8368

FAX # 215 273-4049

Number of Pages (INCLUDING COVER PAGE) 3

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

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Additional message:

Hi Janet,
Attached is a list of requests from the Division. Please give me a call after you have reviewed it with a timeframe you propose to respond.
Thanks
Sandy

NDA 21-128 Children Motrin Cold Suspension

Please submit the following information:
(All the data submitted should be reviewed and analyzed by the Sponsor.)

A. For the two pediatric studies submitted to the NDA.
For the 2 to < 6 year old age group and for the 6 year and older age group, provide:

Listing of adverse event counts in order of decreasing occurrence of the event utilizing COSTART terms.

Listing of adverse event cases by body system and individual COSTART terms, including age, sex, weight, dose, number of doses received, seriousness (serious/non-serious), outcome and relationship to study drug.

B. Marketing History

Clarify if the combination of ibuprofen/pseudoephedrine has ever been marketed, registered and/or licensed in a foreign country either Rx or OTC. If yes, provide:

- date of licensure, marketing status, and country
- dosage strength/concentration, dosing schedule, and use for what age ranges
- whether the drug has ever been withdrawn from the market (if applicable).

C. Safety Profile Data

a) For all combination ibuprofen/pseudoephedrine products, submit safety data from all available sources (spontaneous reports and literature, and any clinical trial information, U.S. and non-U.S.) through January 2000 for all ages.

b) For individual products (ibuprofen and pseudoephedrine) submit safety data from all available sources (spontaneous reports and literature, and any clinical trial information, U.S. and non U.S.) for ages <12. Information for ibuprofen only needs to go back to the time of your last submission for your pediatric products in this age group. Cross reference as applicable to NDA's for pediatric ibuprofen. Pseudoephedrine data should be obtained from 1992 on.

For a and b:

1. Data should be categorized by age group. Please separate out information for the 0 to < 2 years and the 2 to < 12 years old age groups.

2. Adverse event counts should be listed in order of decreasing occurrence of the event utilizing COSTART terms.

3. Adverse event cases should be listed by body system and individual COSTART terms, including age, sex, weight, dose, number of doses received, outcome and relationship to study drug.

4. Poison Control overdose and abuse data should include combination, single ingredients given together and single ingredients separately

5. Provide:

- Separate listings for serious and non-serious adverse events.
- A separate listing for cases in which both drugs were taken concomitantly.
- A separate listing for deaths.
- Case report forms for serious adverse events and deaths.

6. Literature search for safety data (individual products and the combination). Data should be reviewed, abstracted/summarized and analyzed prior to submission; pediatric data should be separated for ages 0 to < 2 years, and 2 to < 12 years of age. The literature search for safety on pseudoephedrine and ibuprofen should be done to correspond to the dates used to obtain the Adverse Events.

NDA 21-128
HFD 550 ID . EL
HFD 550/ ...ater
HFD-550/Cook
HFD-560/Parmelee
HFD-560/L. Hu